Update on Medications With Adverse Skeletal Effects

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On completion of this article, you should be able to (1) identify prescription medications associated with increased risk of fractures, (2) recognize the importance of assessing baseline fracture risk in patients initiating and continuing these medications, and (3) recognize the role of teriparatide in patients at high risk of fracture who must take glucocorticoids.

Patients rely on their primary care physician to manage multiple, often chronic medical conditions that require prescription medications. Balancing the risk to benefit of treatments can be challenging and requires that the primary care physician stay abreast of new information regarding risks and benefits. The number of medications with reported adverse effects on skeletal health is expanding. This review focuses on medications recently added to the list of "bad to the bone" drugs and on recent advances in management of glucocorticoid-induced osteoporosis. A practical approach to assessing and managing the skeletal risks is outlined.

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BMD = bone mineral density; GnRH = gonadotropin-releasing hormone; 5HTT = 5-hydroxytryptamine transporter; PPARγ = peroxisome proliferator–activated receptor gamma; PPI = proton pump inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant

Osteoporosis is a common condition, and its etiology can be multifactorial, with contributions from diet and lifestyle, genetics (including sex and ethnicity), and other medical conditions. Patients with osteoporosis rely on primary care physicians for management of multiple medical conditions in addition to their osteoporosis. Such clinicians must be aware of how prescription medications may adversely affect the skeleton and increase the risk of fractures. The number of prescription medications recognized to increase the risk of osteoporosis or fractures has grown as a result of recent studies (Table 1). They include medications associated with large increases in fracture risk in the individual patient as well as drugs that may not greatly increase individual risk but, because of their widespread use, may substantially affect population risk. This review focuses on some of the medications more recently identified as posing a fracture risk, summarizes the current evidence for their association with low bone mass and fracture, and provides practical advice regarding patient management (Table 2).

GLUCOCORTICOIDS

Any review of medication-induced osteoporosis or fractures must discuss the most common secondary cause of osteoporosis—glucocorticoid therapy.[1] Glucocorticoids decrease bone formation by direct effects on osteoblasts. They also increase osteocyte apoptosis and initially increase the life span of mature osteoclasts. This leads to the well-known early, rapid bone loss associated with use of these medications. Moreover, glucocorticoids have secondary effects that are detrimental to the skeleton, including decreases in intestinal calcium absorption, increases in urinary calcium excretion, hypogonadism, and muscle weakness. Glucocorticoids increase the risk of fracture, especially at cancellous bone sites such as the vertebrae. Fractures often occur at a higher bone density in those taking glucocorticoids than do similar fractures associated with typical postmenopausal osteoporosis. Even "low" doses of oral preparations (<7.5 mg/d of prednisone) may have negative skeletal effects.[2] Potent inhaled and topical glucocorticoids at high doses can have systemic effects, including bone loss. However, these preparations often control an underlying disease and spare the patient exposure to the more devastating effects of systemic glucocorticoids.

Although the main action of glucocorticoids on bone is to decrease bone formation and the bisphosphonates are antiresorptive, not anabolic, agents, trials have proven that bisphosphonates lower the risk of fractures in patients taking glucocorticoids. Therefore, bisphosphonates are the standard medications used to prevent and treat glucocorticoid-induced bone loss. Currently, alendronate, risedronate, and zoledronic acid are approved for this indication on the basis of trial data indicating benefit. A recent active comparator study of zoledronic acid intravenously once yearly and risedronate at 5 mg/d in patients receiving glucocorticoids showed that both bisphosphonates increased bone mineral density (BMD) over baseline. However, those receiving zoledronic acid had significantly greater increases in lumbar spine and femoral neck BMD at 1 year compared with those receiving risedronate.

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TABLE 1. **Medications With Adverse Skeletal Effects**

Drug class	Mechanism
Glucocorticoids	Decreased bone formation
Unfractionated heparin	Decreased bone formation, increased resorption
Aromatase inhibitors	Reduced estrogen production
Gonadotropin-releasing hormone agonists	Hypogonadism
Medroxyprogesterone acetate (depot)	Reduced estrogen levels
Excessive thyroid hormone replacement	Increased bone resorption
Thiazolidinediones	Possible decreased bone formation
Proton pump inhibitors	Possible decreased calcium absorption
Serotonin selective reuptake inhibitors	Inhibition of serotonin transporter
Antiepileptics	Uncertain
Calcineurin inhibitors	Uncertain

TABLE 2. **Prudent Steps in Managing Patients Taking Medications With Potentially Negative Skeletal Effects**

- Assess fracture risk on prescription initiation and renewal
- Recommend lifestyle changes that promote skeletal health (eg, avoid tobacco and excess alcohol, optimize calcium and vitamin D, engage in regular weight-bearing exercise)
- Consider medications with less skeletal impact when fracture risk is high
- Routinely review the ongoing need for medication
- Follow standard osteoporosis treatment recommendations and guidelines
- Reassess bone density and fracture risk 1 year after starting glucocorticoids, AIs, or GnRH agonists in patients not receiving osteoporosis treatments
- Identify patients with a high fracture risk who are receiving glucocorticoids for possible teriparatide treatment
- Regularly reinforce adherence to osteoporosis treatment once initiated

AI = aromatase inhibitor; GnRH = gonadotropin-releasing hormone.

More recently, the anabolic agent teriparatide has been shown to be beneficial in reducing bone loss and the risk of fractures associated with glucocorticoids. In a randomized trial, the effects of teriparatide on BMD and fracture were compared with those of alendronate in men and women taking glucocorticoids.[3] The primary outcome was the change in BMD at the lumbar spine. Secondary outcomes included changes in BMD at the total hip and in markers of bone turnover, the time to changes in BMD, and the incidence of fractures. At the end of 18 months and 36 months, the teriparatide group had significantly greater increases in both spine and hip BMD compared with the alendronate group. The number of vertebral fractures was significantly lower in the teriparatide group. The number of nonvertebral fractures did not differ between the groups. Although cost prevents teriparatide from being recommended for all patients, these results make it reasonable to consider teriparatide in patients with a high risk of fractures who must take oral glucocorticoid medications.

The updated recommendations by the American College of Rheumatology for the prevention and treatment of glucocorticoid-induced osteoporosis highlight the need to assess the baseline risk of fracture and incorporate the dose and anticipated duration of glucocorticoid therapy into treatment decisions regarding osteoporosis prevention and treatment.[4] Patients with a high risk of fracture require osteoporosis treatment even if they are not taking glucocorticoids. If they are taking glucocorticoids, teriparatide therapy should be considered. Although FRAX (World Health Organization Fracture Risk Assessment Tool; available at http://www.sheffield.ac.uk/FRAX/) is an excellent tool for estimating fracture risk in osteoporosis treatment–naive patients, clinical judgment can be used to assign a patient to a fracture risk category.

AROMATASE INHIBITORS

Aromatase inhibitors have emerged as a large part of adjuvant endocrine therapy for breast cancer. Their detrimental skeletal effects, as well as those of medroxyprogesterone acetate and gonadotropin-releasing hormone (GnRH) agonists, are a result of lowered estrogen levels. The association of postmenopausal hypogonadism with osteoporosis and fractures was initially recognized by Fuller Albright in the 1940s. He also performed the first successful "drug trial" with estrogen replacement. Since then, the pivotal role of sex steroids, especially estrogen, in establishing, maintaining, and promoting skeletal integrity in both men and women has been shown in numerous studies.[5] Estrogen suppresses bone resorption by increasing osteoclast apoptosis and reducing the number and activity of osteoclasts. It also promotes bone formation by reducing osteoblast apoptosis and promoting osteoblast differentiation. Residual estrogen levels in postmenopausal women are associated with bone density and fracture risk[6-8]; lower levels equal higher fracture risk. Therefore, it is not surprising that medications that disrupt sex steroid production and lower estrogen levels are associated with negative effects on bone.

Breast cancer treatment trials comparing aromatase inhibitors with tamoxifen show that women treated with any of the 3 aromatase inhibitors (anastrazole, letrozole, exemestane) are at an increased risk of bone loss and that the risk is higher with nonsteroidal preparations (eg, anastrazole and letrozole). Fracture incidence was also higher with anastrozole and letrozole, and a trend toward higher incidence with exemestane compared with tamoxifen was observed. The magnitude of the skeletal risks of aromatase inhibitors may be underestimated because these trials were

active comparator trials with tamoxifen, which has known modest positive effects on BMD. In recent trials, the oral bisphosphonates risedronate[9] and ibandronate[10] and the intravenous bisphosphonate zoledronic acid[11,12] have been shown to prevent bone loss in women with breast cancer who are taking aromatase inhibitors. Preliminary studies also show bone density benefits with denosumab.[13] No trials addressing fracture risk reduction with osteoporosis treatment in the setting of aromatase inhibitor therapy have been reported to date. Treatment recommendations for osteoporosis therapies in the setting of aromatase inhibitors should take into account the baseline fracture risk. Some experts favor a more aggressive management with bisphosphonates for those with osteopenia (defined as T score lower than –1.5).[14]

MEDROXYPROGESTERONE ACETATE

Medroxyprogesterone acetate given as a depot injection every 3 months is an effective contraceptive agent. This medication has been associated with lower estrogen levels and bone loss. The bone loss is most rapid in the first few years of therapy and then continues at a slower rate. Bone mass increases with cessation of the medication,[15] but the degree of recovery and the ultimate bone density after discontinuation may depend on the patient's age at initiation of the medication.[16] A single study examining the risk of fractures in a developmentally disabled population found an increased risk associated with depot medroxyprogesterone acetate use.[17] For most women, the risk of bone loss with depot medroxyprogesterone acetate is not enough to prevent its use, especially given the likelihood of bone recovery with cessation. It seems prudent to advise women receiving this contraceptive to consume adequate calcium and vitamin D and engage in weight-bearing exercise for skeletal health. Women who have a low-trauma fracture while receiving this contraceptive should have assessment of BMD, and those with low bone mass (T score lower than –1.5) should receive counseling about alternative contraceptives and habits that promote bone health. Referral to an osteoporosis expert should be considered if the T score is lower than –2.5.

GnRH AGONISTS

Gonadotropin-releasing hormone agonists act on the pituitary to disrupt the production of sex steroids by the gonads. Bone loss is well recognized in women taking GnRH agonists, usually for treatment of endometriosis. Use of GnRH agonists is increasing not only to treat advanced prostate cancer but also to prevent progression of earlier-stage disease. Cross-sectional and longitudinal studies report that men receiving long-term treatment with GnRH agonists have lower bone mass[18] and that acute bone loss occurs with institution of GnRH agonists.[19] An increase in fracture risk reported in men with prostate cancer treated with GnRH agonists is likely the consequence of bone loss.[20,21] The recognition of bone loss as a consequence of GnRH agonists has resulted in several therapeutic trials of bone antiresorptive agents in men with prostate cancer receiving GnRH agonists. The intravenous bisphosphonates zoledronic acid[22] and pamidronate[23] and the oral bisphosphonate alendronate[24] have recently been proven to be efficacious in preventing bone loss in this patient population. The selective estrogen receptor modulators toremifene[25] and raloxifene[26] have also been shown to be efficacious. Most recently, separate placebo-controlled trials of toremifene[27] and denosumab[28] have demonstrated vertebral fracture risk reduction in osteopenic men receiving androgen deprivation therapy, including GnRH agonists.

Treating men at moderate or high baseline fracture risk with osteoporosis therapies is a prudent and cost-effective strategy.[29] Lower-risk men should be monitored for bone loss with serial BMD measurements.

THIAZOLIDINEDIONES

The negative effect of thiazolidinediones on the skeleton has received increasing attention. Thiazolidinediones are insulin-sensitizing drugs that are agonists of peroxisome proliferator–activated receptor gamma (PPARγ), a nuclear transcription factor that is expressed in bone marrow stromal cells, osteoblasts, and osteoclasts. The PPARγ agonists promote adipogenesis at the expense of osteoblastogenesis. Thus, these drugs have the potential to reduce bone formation by direct action on bone cell differentiation. Indirect actions on bone may also be a factor because PPARγ agonists affect adipose tissue production of adipocytokines that are thought to affect skeletal metabolism. Because of the known role of PPARγ in directing cellular differentiation toward adipocytes and away from osteoblasts, rodent studies as early as 1995 showed detrimental skeletal consequences of thiazolidinediones.[30]

Multiple recent studies in humans have confirmed that these drugs have a potential negative effect on bone. Although most of these studies are cohort or case-control cross-sectional or retrospective analyses, the number of patients is large and the findings are relatively consistent that fracture risk is elevated with both rosiglitazone and pioglitazone and that the risk is higher in postmenopausal women but is also suggested in men concomitantly taking loop diuretics. The risk appears to be dependent on dose.

The Diabetes Outcome Progression Trial (ADOPT) found that women randomized to rosiglitazone had a higher fracture risk than those randomized to metformin or glyburide.[31] Because fractures were not a prespecified end point in ADOPT, the information regarding fractures is limited, but post hoc analyses of earlier clinical trials confirmed these findings. Fractures associated with thiazolidinediones are largely lower extremity fractures, which are not classic osteoporotic fractures and may pose a unique risk to individuals with diabetes. Data regarding the effects of thiazolidinediones on BMD are very limited and only from short-term studies (3-4 months).

No data support the efficacy of osteoporosis treatments in abrogating the effects of thiazolidinediones on fracture risk or bone loss. Until additional data are available, patients in whom thiazolidinedione treatment is initiated should be assessed for their fracture risk and treated according to standard osteoporosis recommendations. Recent revisions by the US Food and Drug Administration to the prescribing information for rosiglitazone regarding heart failure risks are likely to curb the use of this medication. Health care professionals should consider alternatives to thiazolidinediones in patients at high risk of fracture or with established osteoporosis. It is unknown whether the skeletal effects of thiazolidinediones dissipate after cessation of use.

PROTON PUMP INHIBITORS

Proton pump inhibitors (PPIs) are a fairly recent addition to the list of medications with negative skeletal effects. These drugs are widely prescribed, often with the intention of long-term or indefinite use so the potential effect of adverse skeletal events at the population level is large. At high concentrations, omeprazole interacts with the vacuolar adenosine triphosphatases on osteoclasts in vitro and in rodents, suggesting an antiresorptive effect on bones. However, long-term administration to rats resulted in lower bone density. It is clear that gastric acid is important for absorption of the most common form of calcium supplements, calcium carbonate.[32] In fact, short-term omeprazole use in humans decreased serum calcium and urinary calcium levels compared with placebo.[33] A recent study suggested that meal composition, especially the protein content of the meal, may be important to calcium absorption during PPI administration.

The initial human studies investigating acid suppression and fractures were population-based case-control studies that used prescription records and hospital fracture codes.[34] Use of PPIs within the year before the study was associated with a significant increase in overall fracture risk (odds ratio, 1.18) and hip fractures (odds ratio, 1.60). No dose dependency was found for PPIs, and H_2 blocker use was associated with a lower risk of fracture. Other case-control studies have confirmed the association between PPIs and fracture risk, especially hip fractures; demonstrated effects were dependent on duration of use.[35,36] Prospective studies have also shown increased risk of fracture with PPIs.[37,38] The effects of PPIs may differ between men and women and may depend on calcium intake.[38] Studies of less potent acid-reducing agents such as H_2 receptor antagonists have revealed conflicting results on fracture risk, so additional studies are needed to determine whether a relationship exists.

More studies are needed to clarify whether calcium intake can abrogate the negative effects of PPIs and whether standard osteoporosis medications lower fracture risk. In the absence of this information, health care professionals should assess fracture risk in patients taking PPIs, review the ongoing need for the medication, consider alternatives to PPIs such as H_2 blockers when the risk is not clearly elevated, recommend calcium citrate supplements to those taking PPIs who require calcium supplements to meet recommended intake, and institute osteoporosis therapies according to established osteoporosis treatment guidelines.

SEROTONIN SELECTIVE REUPTAKE INHIBITORS

In the past decade, antidepressant drugs have been more frequently prescribed because of the increased public awareness of the symptoms of depression. Selective serotonin reuptake inhibitors (SSRIs) are the most used because of their lower adverse effect profile. Depression has been associated with adverse skeletal events through effects on the hypothalamic-pituitary-adrenal/gonadal axis as well as proinflammatory cytokines. Patients with depression also have frequent comorbid conditions, which could further affect skeletal health, including hypothalamic hypogonadism. The combination of these factors presents challenging confounding variables when trying to study the isolated effects of various antidepressants on bone health.

Concern about antidepressants and their effects on the skeletal system has increased since the discovery of functional serotonergic pathways in bone cells. The 5-hydroxytryptamine transporter (5HTT) is important in regulating serotonin uptake and has been found in osteocytes, osteoblasts, and osteoclasts. In mice, inhibition of the 5HTT by null mutation of the *5HTT* gene altered skeletal architecture, reduced bone mass, and resulted in inferior bone mechanical properties.[39] Growing mice treated with SSRIs showed reduced bone mineral accrual, highlighting the effect of serotonin inhibition on osteoblast function. This leads to 2 important questions: (1) Does SSRI-induced inhibition of 5HTT influence bone health in ado-

lescents prescribed these medications? (2) Do antidepressants reduce BMD enough to increase the risk of fractures in adults?

Multiple studies have examined the effects of SSRIs and tricyclic antidepressants (TCAs) on bone health, with most showing an increased risk of fractures with SSRIs. Older studies tended to have more confounding variables that are better accounted for by newer studies. In the Canadian Multicentre Osteoporosis trial,[40] a prospective cohort study of 5008 adults older than 50 years followed up during a 5-year period for fractures, patients taking SSRIs daily had an increased risk of incident clinical fragility fracture, increased odds of falling, and lower BMD at the hip and spine than those not taking SSRIs. Dosage and duration of treatment with antidepressants were not reported. Another study found the risk of nonvertebral fracture to be 2.35 greater for those currently taking SSRIs than for those not taking SSRIs.[41] The same study found that, during the initial phase of TCA treatment, fracture risk was increased; however, risk was reduced with prolonged exposure. Other studies also highlight the association between SSRI use and lower BMD. In one study, serial total hip BMD decreases were greater in those taking SSRIs (0.82% per year) compared with those taking TCAs (0.47% per year) and those taking neither drug.[42] A cross-sectional study of men older than 65 years found BMD to be lower (3.9% at the hip and 5.9% at the spine) in those taking vs not taking SSRIs, whereas no difference in BMD was noted in those taking vs not taking TCAs.[43] A study of women with a lifetime history of depression also found that SSRI use (mean duration, 34 months) was associated with lower BMD (5.6% at femoral neck, 6.2% at the trochanter, and 4.4% at the forearm).[44]

The preponderance of evidence points to a negative effect of SSRIs on BMD and fracture risk. The higher the affinity of an antidepressant for 5HTT, the higher the risk of fracture.[45] In the absence of trials of osteoporosis treatments, clinicians should assess the fracture risk of patients taking these medications and follow established osteoporosis treatment recommendations.

CONCLUSION

The list of medications exhibiting negative skeletal actions is expanding. For some, the mechanisms have been well defined and treatments have been developed to lessen the negative skeletal effect. For medications recently identified as posing a risk of adverse skeletal effects, additional studies are needed to better assess the risk, define the mechanisms, and evaluate the effect of osteoporosis treatments. In the absence of such evidence, a prudent strategy should be adopted.

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CME Questions About Medications With Adverse Skeletal Effects

1. Which <u>one</u> of the following <u>best</u> describes the effects of teriparatide vs alendronate in treating glucocorticoid-induced osteoporosis?
   a. Greater reduction in hip fractures
   b. Fewer adverse effects
   c. Greater increases in radial bone mineral density (BMD)
   d. Fewer vertebral fractures
   e. Lower bone turnover

2. For a patient receiving long-term proton pump inhibitor (PPI) therapy, which <u>one</u> of the following is the <u>best</u> advice regarding calcium intake?
   a. Increase calcium intake to 2000 mg/d
   b. Chewable calcium carbonate is better absorbed
   c. Calcium citrate does not require acid to be absorbed
   d. Calcium supplements are better than dietary calcium
   e. Calcium found in plant sources is the best dietary source

3. Which <u>one</u> of the following is <u>true</u> about gonadotropin-releasing hormone (GnRH) agonist therapy in men with prostate cancer?
   a. It induces hypercalciuria
   b. It decreases intestinal calcium absorption
   c. It increases risk of fractures
   d. It lowers bone turnover
   e. Its effects can be prevented by vitamin D

4. A 62-year-old woman with recently diagnosed breast cancer will soon begin treatment with letrozole. Which <u>one</u> of the following is the <u>best next</u> step in her management?
   a. Measure calcium, phosphorus, and parathyroid hormone levels
   b. Measure BMD
   c. Perform radiography of the lumbar spine
   d. Measure 1,25-dihydroxyvitamin D levels
   e. Measure 24-hour urinary calcium excretion

5. A 49-year-old woman presents for follow-up of depression for which selective serotonin reuptake inhibitor (SSRI) therapy was initiated 1 year previously. Which <u>one</u> of the following is <u>most important</u> to assessing her skeletal health?
   a. Ask about libido
   b. Assess her depression
   c. Ask about weight gain
   d. Ask about adverse effects of SSRIs
   e. Ask about kidney stone history

This activity was designated for 1 AMA PRA Category 1 Credit(s).™

Because the Concise Review for Clinicians contributions are now a CME activity, the answers to the questions will no longer be published in the print journal. For CME credit and the answers, see the link on our Web site at mayoclinicproceedings.com.